

Amendments to the Claims

1-41. (Cancelled)

5 42. (New) A small interfering RNA (siRNA) comprising 15-25 nucleotides complementary to a target nucleic acid sequence, wherein the RNA comprises at least one internucleoside linkage chosen from ribo-N3'→P5' phosphoramidate (NP) and ribo-N3'→P5' thiophosphoramidate (NPS) linkages.

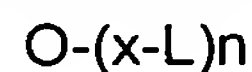
10 43. (New) The small interfering RNA according to Claim 42, wherein all of the internucleoside linkages are chosen from ribo-N3'→P5' phosphoramidate (NP) and ribo-N3'→P5' thiophosphoramidate (NPS) linkages.

15 44. (New) The small interfering RNA according to Claim 42, wherein said small interfering RNA is in a form chosen from the single-stranded form comprising the antisense strand, and the double-stranded form comprising both sense and antisense strands.

20 45. (New) The small interfering RNA according to Claim 42, wherein the RNA further comprises at least one covalently conjugated lipid moiety.

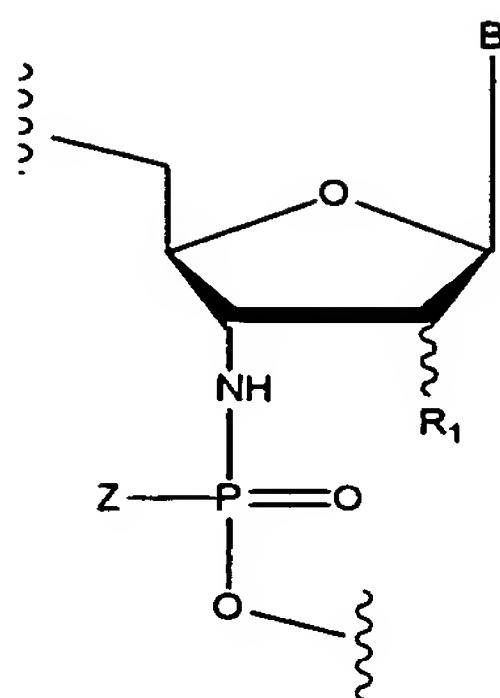
25 46. (New) The small interfering RNA according to Claim 45, wherein one lipid moiety is covalently conjugated to the 5' or 3' terminus of the RNA, and the lipid moiety is chosen from fatty acids, sterols, and hydrocarbons.

47. (New) A compound comprising the structure:



wherein

-O is an oligonucleotide of formula:



wherein R_1 is chosen from fluorine and OR_2 , R_2 is chosen from hydrogen and lower alkyl, B is chosen from purines, pyrimidines, and analogs thereof, and Z is chosen from oxygen and sulfur, and further wherein the oligonucleotide comprises a sequence of 15 to 25 bases, and said sequence is at least partially complementary to a selected target sequence;

-L is a lipid moiety;

-x is an optional linker; and

n is an integer ranging from 1 to 5, wherein if $n > 1$, each additional (x-L) component may be, independently, the same or different.

48. (New) The compound according to Claim 47, wherein L is a lipid chosen from substituted and unsubstituted fatty acids and sterols; or wherein L is chosen from substituted and unsubstituted hydrocarbons.

49. (New) The compound according to Claim 48, wherein L is chosen from fatty acids substituted with at least one fluorine; or wherein L is chosen from hydrocarbons substituted with at least one fluorine

50. (New) The compound according to claim 47, wherein at least 60% of the nucleobases in the oligonucleotide are ribonucleobases.

51. (New) The compound according to Claim 47, wherein said compound is an antisense strand of a small interfering RNA.

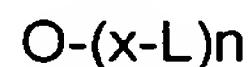
52. (New) A method for effecting the post-transcriptional silencing of at least one gene, comprising administering to a mammal in need of such post-transcriptional silencing at least one small interfering RNA comprising 15-25 nucleotides complementary to a target nucleic acid sequence, wherein the RNA comprises at least

one internucleoside linkage chosen from ribo-N3'→P5' phosphoramidate (NP) and ribo-N3'→P5' thiophosphoramidate (NPS) linkages.

53. (New) The method according to Claim 52, wherein the small interfering RNA
5 further comprises at least one covalently conjugated lipid moiety.

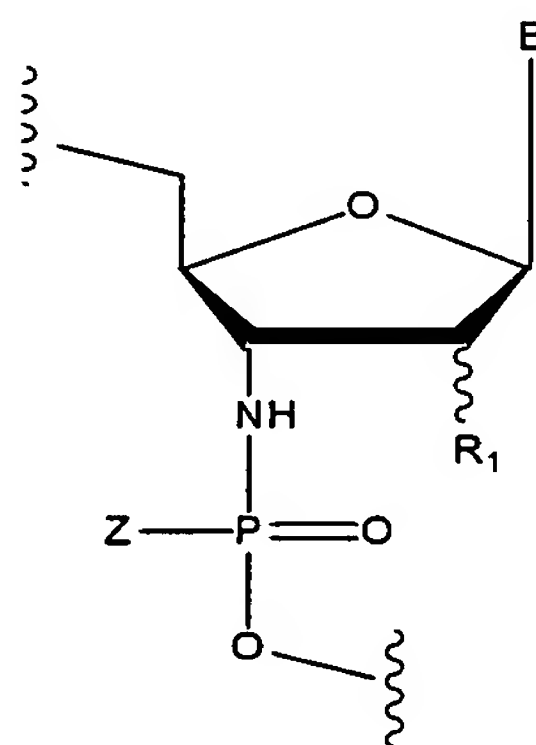
54. (New) The method of claim 52, wherein the at least one gene encodes at least one mRNA chosen from cellular mRNAs and viral mRNAs; or wherein the at least one gene is an oncogene; or wherein the at least one gene is a viral gene.

55. (New) A method for effecting the post-transcriptional silencing of at least one gene, comprising administering to a mammal in need of such post-transcriptional silencing at least one compound comprising the structure:



15 wherein

-O is an oligonucleotide of formula:



wherein R_1 is chosen from fluorine and OR_2 , R_2 is chosen from hydrogen and lower alkyl, B is chosen from purines, pyrimidines, and analogs thereof, and Z is chosen from oxygen and sulfur, and further wherein the oligonucleotide comprises a sequence of 15 to 25 bases, and said sequence is at least partially complementary to a selected target sequence;

-L is a lipid moiety;

-x is an optional linker; and

25 n is an integer ranging from 1 to 5, wherein if $n > 1$, each additional (x-L) component may be, independently, the same or different.

56. (New) The method according to claim 55, wherein the at least one gene

encodes at least one mRNA chosen from cellular mRNAs and viral mRNAs; or wherein the at least one gene is an oncogene; or wherein the at least one gene is a viral gene.

57. (New) The small interfering RNA according to Claim 44, wherein said small
5 interfering RNA is in single-stranded form, is at least 17 nucleotides in length, comprises at least one internucleoside linkage chosen from ribo-3'→P5' phosphoramidate (NP) and ribo-N3'→P5' thiophosphoramidate (NPS) linkages, and is effective to inhibit the expression of an endogenous mammalian target RNA sequence.

10 58. (New) The single-stranded small interfering RNA according to Claim 57, wherein the small interfering RNA further comprises at least one covalently conjugated lipid moiety

15 59. (New) The single-stranded small interfering RNA according to Claim 57, wherein the target RNA sequence is encoded by a human gene.

20 60. (New) The small interfering RNA according to Claim 44, wherein said small interfering RNA is in double-stranded form, is at least 17 basepairs in length, comprises at least one internucleoside linkage chosen from ribo-3'→P5' phosphoramidate (NP) and ribo-N3'→P5' thiophosphoramidate (NPS) linkages, and is effective to inhibit the expression of an endogenous mammalian target RNA sequence.

25 61. (New) The double-stranded small interfering RNA according to Claim 60, wherein the target RNA sequence is encoded by a human gene.

62. (New) The double-stranded small interfering RNA according to Claim 60, wherein the RNA further comprises at least one covalently conjugated lipid moiety.

30 63. (New) A small interfering RNA as recited in claim 42, wherein said target nucleic acid sequence is a human immunodeficiency virus (HIV) gene, such that said siRNA modulates expression of said HIV gene.

35 64. (New) The small interfering RNA according to Claim 63, wherein the small interfering RNA further comprises at least one covalently conjugated lipid moiety.

65. (New) A small interfering RNA as recited in claim 42, wherein said target nucleic acid sequence is a beta site APP-cleaving enzyme (BACE) gene, such that said siRNA modulates expression of said BACE gene.

5 66. (New) The small interfering RNA according to Claim 65, wherein the small interfering RNA further comprises at least one covalently conjugated lipid moiety.

67. (New) A small interfering RNA as recited in claim 42, wherein said target nucleic acid sequence is an EGFR gene, such that said siRNA modulates expression of
10 said EGFR gene.

68. (New) The small interfering RNA according to Claim 67, wherein the small interfering RNA further comprises at least one covalently conjugated lipid moiety.

15 69. (New) A small interfering RNA as recited in claim 42, wherein said target nucleic acid sequence encodes K-Ras, such that said siRNA that modulates expression of said K-Ras.

70. (New) The small interfering RNA according to Claim 69, wherein the small
20 interfering RNA further comprises at least one covalently conjugated lipid moiety.

71. (New) A small interfering RNA as recited in claim 42, wherein said target nucleic acid sequence is a prostaglandin D2 receptor (PTGDR) gene, such that said siRNA modulates expression of said PTGDR gene.
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72. (New) The small interfering RNA according to Claim 71, wherein the small interfering RNA further comprises at least one covalently conjugated lipid moiety.

73. (New) A small interfering RNA as recited in claim 42, wherein said target
30 nucleic acid sequence is an ADORA1 gene, such that said siRNA modulates expression of said ADORA1 gene.

74. (New) The small interfering RNA according to Claim 73, wherein the small interfering RNA further comprises at least one covalently conjugated lipid moiety.
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